

Docket No.: 03-34US
Serial No. 10/777,523

REMARKS

This submission is in response to the Office Action, dated October 27, 2005, a response to which is due on January 27, 2006. Since this response is filed within the three-month shortened statutory period of time set for response, no extension of time is necessary. Favorable consideration is respectfully requested in view of the following Amendments and Remarks.

I. STATUS OF THE CLAIMS:

Claims 1-6 and 8-44 were pending. In the Response to Restriction Requirement and Preliminary Amendment, Applicant withdrew claims 36-39 from consideration as being directed to a nonelected invention. In the instant Office Action, the Examiner made final the restriction requirement and election of species requirement. The Examiner withdrew claims 16-18 and 42-44 from consideration as being directed to nonelected species, and claims 25-35 from consideration as being directed to nonelected inventions. Therefore, claims 1-6, 8-24 and 40-44 are pending and under examination. Applicant respectfully requests that claims 16-18 and 42-44 be rejoined and examined upon examination and allowance of the claims with respect to the elected species. Applicant also respectfully requests reconsideration and rejoinder of method claims 25-39, as will be discussed further below. Applicant expressly reserves his right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application.

New claim 45 has been added. Support for the new claim is found, *inter alia*, in claim 32 as filed. Accordingly, upon entry of this amendment, claims 1-6, 8-24 and 40-45 are pending. No new matter has been introduced by way of these amendments.

II. RESTRICTION REQUIREMENT:

In the Requirement for Restriction, the Examiner required restriction between the following three groups of claims:

- I. claims 1-24, directed to a composition, classified in class 210, subclass 198.2;
- II. claims 25-35, directed to a method of modifying an inorganic substrate, classified in class 210, subclass 656; and.

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III. claims 36-39, directed to a method of separating, classified in class 210, subclass 635.

The claims of Group III have been withdrawn from consideration. However, Applicant urges the Examiner to reconsider the decision to restrict the inventions of groups I and II.

The Examiner stated that the inventions of groups I and II are related as process of making and product made. Citing the Manual of Patent Examining Procedure ("MPEP") § 806.05(f), the Examiner stated that the inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process. The Examiner alleged that the product as claimed can be made by another and materially different process, for example it could be made by a reaction in a stirred chemical reactor.

In the instant Office Action, the Examiner stated that there was no link between the process of making claims and product claims. Applicant respectfully points out that claim 1 as amended recites a method step, and no longer encompasses additional materially different processes for making the claimed product. In view of this limitation from the claim's original full scope, Applicant believes that the amended product claims should be examined together with the method claims from which that method step was incorporated. In particular, the Examiner has searched for and cited art relevant to the method claims in the instant Office Action. Accordingly, Applicant believes that the additional examination of the method claims would not present an undue burden on the Examiner, and requests that the two groups of claims be examined together.

III. RESPONSE TO REJECTIONS UNDER 35 U.S.C. 103(a)

The Examiner has cited an extensive list of references and alleged that the pending claims are obvious over each of Abbott (U.S. Patent No. 4,298,500, hereinafter "Abbott"), Cabrera (U.S. Patent No. 5,104,547, hereinafter "Cabrera"), Neue (U.S. Patent No. 5,374,755, hereinafter "Neue"), Nau (U.S. Patent No. 6,071,410, hereinafter "Nau"), Liu (U.S. Patent No. 6,645,378, hereinafter "Liu") and Huang ((2002) *Anal. Sci.* 18, 69-72, hereinafter "Huang") in view of Karger (U.S. Patent No. 4,996,343, hereinafter "Karger") and Fairbank ((1999) *J. Chromatog.* 830, 285-291, hereinafter "Fairbank"), and further in view of Kirkland (U.S. Patent No. 5,869,724, hereinafter "Kirkland") and Ng (U.S. Patent No. 6,296,768, hereinafter "Ng"). Applicant respectfully traverses these rejections.

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Applicant has discovered through diligent efforts a method of preparing stationary phases possessing superior separation and stability characteristics. The presently claimed invention provides superior results in the form of superior peak shapes, superior analyte separations, superior stability to acidic *and basic* solvent conditions, and superior chromatographic characteristics. In particular, the stationary phases developed by Applicant exhibit, *inter alia*, superior peak symmetry, with a total absence of tailing and peak asymmetry that is so problematic in other bonded phases, an almost undetectable affinity for base relative to alcohol, remarkable selectivity between basic analytes, low residual silanol activity, and base deactivation. The stationary phases of the instant specification were tested for stability *at both pH 1.5 and at pH 10* for at least 1500 hours and showed superior stability: the variation in retention times, peak symmetry and retention factors was less than 3% for 1000 hours, and less than 5% for 3000 hours, and thus demonstrate greater stability than the compositions of the prior art cited by the Examiner. In addition, the presently claimed stationary phases are prepared using methods that closely control the amount of water on the substrate surface that can participate in the silanization reaction, thereby providing superior reproducibility in preparation of the phases, as well as superior reaction control, thereby providing superior stability and low residual silanol activity. These superior and unexpected results are not taught by the prior art compositions and methods cited. Therefore neither alone nor in combination can the references cited render the pending claims obvious.

The rejections are addressed in greater detail as follows:

Claims 1-6, 8-15, 19, 23, 24, 40 and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in view of Karger and Fairbank. The Examiner stated that at best, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in reciting use of an equilibrated substrate. The Examiner stated that Karger discloses that use of an equilibrated silica aids in reproducibility and stability, and that Fairbank discloses that there is an optimum humidity level and that shorter equilibration times give poor reproducibility. According to the Examiner, it would have been obvious to use an equilibrated substrate in each of Abbott, Cabrera, Neue, Nau, Liu, and Huang because Karger discloses that use of an equilibrated silica aids in reproducibility and stability, and Fairbank discloses that there is an optimum humidity level and that shorter equilibration times give poor reproducibility.

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Applicant respectfully traverses this rejection. In contrast to the Examiner's assertion, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in additional respects than reciting use of an equilibrated substrate. In addition, the combination of Abbott, Cabrera, Neue, Nau, Liu, and Huang with Karger or Fairbank would not render obvious the pending claims. Each reference is discussed and the rejections addressed below.

Abbott teaches a mixed phase composition made of a porous particle "to less than the maximum number of sterically available active sites of which there is covalently bonded a first residue [...], as a result of which the first residues are spaced more than about 20 Angstroms apart." The spaced residues are achieved by performing the reaction at an at least 10 fold excess of reactive sterically available sites on the silica relative to the residue forming reagent, an organosilane. At this low reactant density, many residual silanol residues would be present, producing a chromatography sorbent incapable of the stability and superior separations, especially for basic analytes, provided by the present compositions.

Cabrera describes preparation of a cyclodextrin derivatized support, wherein the cyclodextrin is bonded via a carbamic acid group, provided by reacting a chloroformic acid ester cyclodextrin with an aminosilane or with a support modified by a silanization reaction with amino groups.

Neue describes carbamate compounds and reversed phase materials comprising a silica substrate modified with a modified allylcarbamate compound, including cyanoalkyl, tertiary butyl, dibutyl, octyl, etc., which may be endcapped with a short chain alkyl silane. The compositions are alleged to provide shielding from undesirable interactions with silanols. Compared with the inventive compositions described in the instant specification however, the stationary phases exhibit tailing and broadening, indicating that the problem of undesirable interactions with unmodified silanols has not been solved, despite Neue's assertions to the contrary. In contrast, the compositions prepared according to the pending claims exhibit a total absence of tailing and peak asymmetry, even for compounds with longer retention times. [See paragraph 158 of Applicant's published application, and compare Neue's Figure 4b with Figure 11C of the instant specification, and Neue's Figure 2b with Figure 11A of the instant specification.]

Nau describes a method for recovering an organic solute from a predominantly aqueous solution, and water wettable sorbent materials for use in solid phase extractions. The sorbent can be

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silica bearing alkyl urethane surface groups. According to Nau, the preparation of silica required only drying with heat before reacting with the silyl alkyl urethane with the silica surface.

Liu describes a modified silica support having a polar phase bound to its surface and suitable for use for chromatographic separations. The compositions of Liu are reported to exhibit decreased interaction with basic analytes due to shielding of the polar groups on the silica surface. The compositions of Liu are also reported to be stable even under harsh chromatographic conditions, such as 1% TFA at 50°C (40L at 1 mL/min), however stability to basic conditions was not demonstrated. The time to 40L, the volume tested at that flow rate, is approximately 667 hours. The stability of the compositions of the instant specification were tested for at least 1500 hours and showed superior stability, e.g., variation in retention times, peak symmetry and retention factors was less than 3% for 1000 hours, and less than 5% for 3000 hours, and thus demonstrated greater stability than the compositions of Liu [see Figures 3A-D and 4A-D of the instant specification and compare with Liu Figure 5].

Huang describes a process for preparing an alkylamide phase for reversed phase HPLC. The alkylamide phase was reported to weaken the interaction between basic analytes and residual silanol groups on the silica surface. Column stability was assessed by comparing the retention factors of the alkylamide phase with a conventional C₈ phase.

Karger teaches a method for bonding organosilanes to silica comprising the steps of "placing a controlled amount of water on the surface of the silica particles to be coated, coating the surface of the silica particles uniformly with at least one alkoxysilane capable of forming at least two bonds with the silica surface via the silicon atom of the alkoxysilane, and finally causing the alkoxysilane to react with the silica surface and crosslink and polymerize in a controlled manner, by heating the alkoxysilane-and-water-coated silica in the presence of vapors of a basic catalyst in the absence of solvent." In other words, Karger *appears to teach* that a controlled amount of water be placed on the silica surface, but then *teaches the opposite*, that the silica is subjected to reduced pressure or vacuum to remove some of the water, thus altering the amount of water present on the surface from the equilibration step to an unknown extent, before performing the silanization reaction. Thus, Karger *teaches away* from the present claims because it de-emphasizes the importance of control over the amount of surface bound water. The silanization reaction described by Karger does not

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provide the control and reproducibility taught by the present claims, and the combination of Karger with additional references also produces a different composition than claimed that would not exhibit the superior stability and retention characteristics observed for the claimed stationary phases.

An additional distinguishing feature is that Karger teaches that the silanization is performed on the surface of the silica, not a solution phase reaction as described in the instant specification. Karger also teaches that the reaction is performed in the presence of a basic catalyst, and that bonding, polymerization and crosslinking then occur directly on the surface. One skilled in the art would recognize that utilizing a surface reaction and a gas phase catalyst would provide significantly different reaction kinetics than those described in the pending claims. The methods described by Karger thus provide less control over the silanization reaction than the claimed methods, and the resulting compositions are distinguishable. For these additional reasons, Karger *teaches away* from the claimed invention.

Fairbank teaches that the amount of adsorbed water needed for horizontal polymerization of trichlorosilanes can be investigated using porous silica gel. The relative humidity to which the silica was exposed was shown to be important in determining the coverage of the silica substrate. NMR characterization showed that 50% humidity was better than 30% or 40% relative humidities for preparing extensively cross-linked monolayers. Zone tailing during HPLC performed on the silica was observed at a relative humidity of 40% but was minimized at 50%, indicating that 50% was the optimal humidity for dense horizontal polymerization of trichlorosilanes, while 60% produced excess polymerization of reagent beyond that which could attach to the surface. No retention was observed at 30% relative humidity, indicating that there was significant interaction of the analyte with the silica substrate, i.e., an increase in surface charge density occurred due to an increase in the amount of exposed silica. Thus, Fairbank *teaches away* from the present claims because it indicates that relative humidities below 50% are not optimal for horizontal polymerization of trichlorosilanes and may result in inadequate coverage of the silica surface with the silane.

First of all, the primary references (Abbott, Cabrera, Nau, Neue, Li and Huang) are not combinable with Karger because the primary references relate to solution phase reactions, while Karger relates to a solid phase reaction. The process taught by Karger involves reacting the silane with the silica surface after treatment with reduced pressure to remove solvent and some of the

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water, that is the reaction is performed without solvent. Therefore, Karger teaches incompatible processes with respect to the primary references, i.e., solution phase versus solid phase reactions, which one skilled in the art would recognize as teaching very different reaction kinetics, applications and objectives. Further, Abbott teaches that the process for manufacture of the composition includes reacting the reagent from which the first residue is formed with an aqueous slurry of the particle, while Karger teaches that the silica is first equilibrated at low relative humidity and then treated with reduced pressure to remove solvent and some of the water, and therefore the reaction performed by Abbott in the presence of water would be completely inconsistent with the process taught by Karger. Therefore, the references are not combinable.

Further, even if Abbott (as well as the other primary references) and Karger are combinable, the combined teachings would not provide the claimed invention. The combination of Abbott and Karger provides for a composition having a submaximal density of silanes after equilibrating the silica with a controlled amount of water, coating the silica with organosilane to less than maximum number of sterically available sites exposing the coated silica to reduced pressure or vacuum and then performing the silanization reaction in the presence of a basic catalyst. However, this is not the claimed invention. In fact this combination of references *teaches away* from the pending claims because Abbott suggests that greater spacing of silanes, e.g., lower silane densities, are preferable for performing chromatographic separations. However the pending claims do not rely on submaximal coating densities. In fact, the present specification teaches the opposite goal from submaximal coating densities, because such substrates would inherently present problems due to the high silanol content resulting from the spacing of silanes on the particle surfaces. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Abbott in view of Karger has been overcome and respectfully requests withdrawal of the rejection.

Similarly, Abbott in view of Fairbank describes a method of preparing a submaximal density of silanes after equilibrating the silica with a controlled amount of water of 30%, 40%, 50% or 60%, and teaches that using a relative humidity below 50% provides less than optimal coverage of the silica surface with silanes. Further, Abbott in view of Fairbank *teaches away* from the pending claims because it suggests that using a relative humidity below 50% results in poor silica coverage and poor performance characteristics in chromatographic applications. In contrast, the claimed

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invention provides excellent retention characteristics, stability and reproducibility, resulting from the superior methods of preparation, which are not characteristics of the compositions taught by the prior art references. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Abbott in view of Fairbank has been overcome and respectfully requests withdrawal of the rejection.

The combination of Cabrera and Karger describes a cyclodextrin derivatized silica support, wherein the cyclodextrin is bonded to the silica via a carbamic acid group, the bonding reaction being performed after equilibrating the silica with a controlled amount of water, coating the silica with the cyclodextrin derivatized silane or an aminosilane, exposing the coated silica to reduced pressure or vacuum and then performing the silanization reaction in the presence of a basic catalyst. However, this is not the claimed invention. Karger teaches that equilibration is performed and then the silica is further treated with reduced pressure or vacuum to remove some of the water, and therefore the silica is no longer equilibrated with a controlled amount of water. Thus, Karger *teaches away* from the present claims because it de-emphasizes the importance of control over the amount of surface bound water. The silanization reaction described by Karger does not provide the control and reproducibility taught by the present claims, and the combination of Cabrera and Karger produces a different composition than claimed and would not exhibit the superior stability and retention characteristics observed for the claimed stationary phases. Further, Karger teaches utilizing a surface reaction of silane on the surface of the silica, not a solution phase reaction, and using a gaseous catalyst, and in these manners also *teaches away* from the claimed invention. One skilled in the art would recognize that utilizing a surface reaction and a gas phase catalyst would provide significantly different reaction kinetics than those described in the pending claims. The methods described by Karger thus provide less control over the silanization reaction than the claimed methods, and the resulting compositions are distinguishable. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Cabrera in view of Karger has been overcome and respectfully requests withdrawal of the rejection.

Similarly, the combination of Cabrera and Fairbank does not yield the pending claims. The combination of Cabrera and Fairbank would describe a cyclodextrin derivatized silica support, wherein the cyclodextrin is bonded to the silica via a carbamic acid group, the bonding reaction

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being performed after equilibrating the silica with 50% relative humidity to provide the optimal horizontal polymerization reaction and not using a relative humidity below 50% because that provides less than optimal coverage of the silica surface with silanes. However, this is not the claimed invention. Further, Cabrera in view of Fairbank *teaches away* from the pending claims because it suggests that using a relative humidity below 50% results in poor silica coverage and poor performance characteristics in chromatographic applications. In contrast, the claimed invention provides excellent retention characteristics, stability and reproducibility, resulting from the superior methods of preparation, which are not characteristics of the compositions taught by the prior art references. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Cabrera in view of Fairbank is overcome and respectfully requests withdrawal of the rejection.

Neue describes carbamate compounds and reversed phase materials comprising a silica substrate modified with a modified allylcarbamate compound, including cyanoalkyl, tertiary butyl, dibutyl, octyl, etc., which may be endcapped with a short chain alkyl silane. The combination of Neue and Karger describes a silica substrate modified with a modified allylcarbamate compound, wherein the modified allylcarbamate compound is bonded to the silica, the bonding reaction being performed after equilibrating the silica with a controlled amount of water, coating the silica with the modified allylcarbamate compound, exposing the coated silica to reduced pressure or vacuum and then performing the silanization reaction in the presence of a basic catalyst. However, this is not the claimed invention. Karger teaches that equilibration is performed and then the silica is further treated with reduced pressure or vacuum to remove some of the water, and therefore the silica is no longer equilibrated with a controlled amount of water. Thus, Karger *teaches away* from the present claims because it de-emphasizes the importance of control over the amount of surface bound water. The silanization reaction described by Karger does not provide the control and reproducibility taught by the present claims, and the combination of Neue and Karger produces a different composition than claimed and would not exhibit the superior stability and retention characteristics observed for the claimed stationary phases. Further, Karger teaches utilizing a surface reaction of silane on the surface of the silica, not a solution phase reaction, and using a gaseous catalyst, and in these manners also *teaches away* from the claimed invention. One skilled in the art would recognize that utilizing a

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surface reaction and a gas phase catalyst would provide significantly different reaction kinetics than those described in the pending claims. The methods described by Karger thus provide less control over the silanization reaction than the claimed methods, and the resulting compositions are distinguishable. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Neue in view of Karger has been overcome and respectfully requests withdrawal of the rejection.

Similarly, the combination of Neue and Fairbank does not yield the pending claims. The combination of Neue and Fairbank describes a silica substrate modified with a modified allylcarbamate compound, the bonding reaction being performed after equilibrating the silica with 50% relative humidity to provide the optimal horizontal polymerization reaction and not using a relative humidity below 50% because that provides less than optimal coverage of the silica surface with silanes. However, this is not the claimed invention. Further, Neue in view of Fairbank *teaches away* from the pending claims because it suggests that using a relative humidity below 50% results in poor silica coverage and poor performance characteristics in chromatographic applications. In contrast, the claimed invention provides excellent retention characteristics, stability and reproducibility, resulting from the superior methods of preparation, which are not characteristics of the compositions taught by the prior art references. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Neue in view of Fairbank is overcome and respectfully requests withdrawal of the rejection.

The combination of Nau and Karger describes a method for recovering an organic solute from a predominantly aqueous solution, and water wettable sorbent materials including silica for use in solid phase extractions bearing alkyl urethane surface groups, wherein the alkyl urethane surface groups are bonded to the silica, the bonding reaction being performed after equilibrating the silica with a controlled amount of water, coating the silica with the alkyl urethane trialkoxysilanes, exposing the coated silica to reduced pressure or vacuum and then performing the silanization reaction in the presence of a basic catalyst. However, this is not the claimed invention. Karger teaches that equilibration is performed and then the silica is further treated with reduced pressure or vacuum to remove some of the water, and therefore the silica is no longer equilibrated with a controlled amount of water. Thus, Karger *teaches away* from the present claims because it de-

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emphasizes the importance of control over the amount of surface bound water. The silanization reaction described by Karger does not provide the control and reproducibility taught by the present claims, and the combination of Nau and Karger produces a different composition than claimed and would not exhibit the superior stability and retention characteristics observed for the claimed stationary phases. Further, Karger teaches utilizing a surface reaction of silane on the surface of the silica, not a solution phase reaction, and using a gaseous catalyst, and in these manners also *teaches away* from the claimed invention. One skilled in the art would recognize that utilizing a surface reaction and a gas phase catalyst would provide significantly different reaction kinetics than those described in the pending claims. The methods described by Karger thus provide less control over the silanization reaction than the claimed methods, and the resulting compositions are distinguishable. In addition, Nau teaches away from the present claims because it teaches that the silica requires only drying with heat before reacting with the silane. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Nau in view of Karger has been overcome and respectfully requests withdrawal of the rejection.

Similarly, the combination of Nau and Fairbank does not yield the pending claims. The combination of Nau and Fairbank describes a method for recovering an organic solute from a predominantly aqueous solution, and water wettable sorbent materials including silica for use in solid phase extractions bearing alkyl urethane surface groups, the bonding reaction being performed after equilibrating the silica with 50% relative humidity to provide the optimal horizontal polymerization reaction and not using a relative humidity below 50% because that provides less than optimal coverage of the silica surface with silanes. However, this is not the claimed invention. Further, Nau in view of Fairbank *teaches away* from the pending claims because it suggests that using a relative humidity below 50% results in poor silica coverage and poor performance characteristics in chromatographic applications. In contrast, the claimed invention provides excellent retention characteristics, stability and reproducibility, resulting from the superior methods of preparation, which are not characteristics of the compositions taught by the prior art references. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Nau in view of Fairbank is overcome and respectfully requests withdrawal of the rejection.

The combination of Liu and Karger describes a modified silica support having a polar phase

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bound to its surface and suitable for use for chromatographic separations, the bonding reaction being performed after equilibrating the silica with a controlled amount of water, coating the silica with the silanes, exposing the coated silica to reduced pressure or vacuum and then performing the silanization reaction in the presence of a basic catalyst. However, this is not the claimed invention. Karger teaches that equilibration is performed and then the silica is further treated with reduced pressure or vacuum to remove some of the water, and therefore the silica is no longer equilibrated with a controlled amount of water. Thus, Karger *teaches away* from the present claims because it de-emphasizes the importance of control over the amount of surface bound water. The silanization reaction described by Karger does not provide the control and reproducibility taught by the present claims, and the combination of Liu and Karger produces a different composition than claimed and would not exhibit the superior stability and retention characteristics observed for the claimed stationary phases. The compositions of Liu are reported to exhibit decreased interaction with basic analytes due to shielding of the polar groups on the silica surface. However, the presently claimed invention provides superior results than those provided by the compositions of Liu. In addition, the compositions of Liu are reported to be stable even under harsh chromatographic conditions. However, as discussed above, the stability of the compositions of the instant specification were tested for over twice as long, at least 1500 hours, and showed superior stability, e.g., variation in retention times, peak symmetry and retention factors was less than 3% for 1000 hours, and less than 5% for 3000 hours, *even at pH 1.5 and pH 10*, and thus demonstrated greater stability than the compositions of Liu [see Figures 3A-D and 4A-D of the instant specification and compare with Liu Figure 5]. *Thus the presently claimed invention exhibits superior and unexpected results in comparison with the compositions described by Liu.*

Further, Karger teaches utilizing a surface reaction of silane on the surface of the silica, not a solution phase reaction, and using a gaseous catalyst, and in these manners also *teaches away* from the claimed invention. One skilled in the art would recognize that utilizing a surface reaction and a gas phase catalyst would provide significantly different reaction kinetics than those described in the pending claims. The methods described by Karger thus provide less control over the silanization reaction than the claimed methods, and the resulting compositions are distinguishable. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Liu in view of

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Karger has been overcome and respectfully requests withdrawal of the rejection.

Similarly, the combination of Liu and Fairbank does not yield the pending claims. The combination of Liu and Fairbank describes a modified silica support having a polar phase bound to its surface and suitable for use for chromatographic separations, the bonding reaction being performed after equilibrating the silica with 50% relative humidity to provide the optimal horizontal polymerization reaction and not using a relative humidity below 50% because that provides less than optimal coverage of the silica surface with silanes. However, this is not the claimed invention. Further, Liu in view of Fairbank *teaches away* from the pending claims because it suggests that using a relative humidity below 50% results in poor silica coverage and poor performance characteristics in chromatographic applications. In contrast, the claimed invention provides excellent retention characteristics, stability and reproducibility, resulting from the superior methods of preparation, which are not characteristics of the compositions taught by the prior art references. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Liu in view of Fairbank is overcome and respectfully requests withdrawal of the rejection.

The combination of Huang and Karger describes a process for preparing an alkylamide phase for reversed phase HPLC, the bonding reaction being performed after equilibrating the silica with a controlled amount of water, coating the silica with the silanes, exposing the coated silica to reduced pressure or vacuum and then performing the silanization reaction in the presence of a basic catalyst. However, this is not the claimed invention. Karger teaches that equilibration is performed and then the silica is further treated with reduced pressure or vacuum to remove some of the water, and therefore the silica is no longer equilibrated with a controlled amount of water. Thus, Karger *teaches away* from the present claims because it de-emphasizes the importance of control over the amount of surface bound water. The silanization reaction described by Karger does not provide the control and reproducibility taught by the present claims, and the combination of Huang and Karger produces a different composition than claimed and would not exhibit the superior stability and retention characteristics observed for the claimed stationary phases.

The compositions of Huang are reported to weaken the interaction between basic analytes and residual silanol groups on the silica surface. Column stability *at pH 2.5 and 7.5* was assessed by comparing the retention factors of the alkylamide phase with a conventional C₈ phase. However, the

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presently claimed invention provides superior results than those provided by the compositions of Huang, both in terms of stability and chromatographic performance. As discussed above, the stability of the compositions of the instant specification were tested for at least 1500 hours, and showed superior stability, e.g., variation in retention times, peak symmetry and retention factors was less than 3% for 1000 hours, and less than 5% for 3000 hours, *even at pH 1.5 and pH 10*, and thus demonstrated greater stability than the compositions of Liu [see Figures 3A-D and 4A-D of the instant specification and compare with Liu Figure 5]. Thus the presently claimed invention exhibits *superior results* in comparison with the compositions described by Huang.

Further, Karger teaches utilizing a surface reaction of silane on the surface of the silica, not a solution phase reaction, and using a gaseous catalyst, and in these manners also *teaches away* from the claimed invention. One skilled in the art would recognize that utilizing a surface reaction and a gas phase catalyst would provide significantly different reaction kinetics than those described in the pending claims. The methods described by Karger thus provide less control over the silanization reaction than the claimed methods, and the resulting compositions are distinguishable. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Huang in view of Karger has been overcome and respectfully requests withdrawal of the rejection.

Similarly, the combination of Huang and Fairbank does not yield the pending claims. The combination of Huang and Fairbank describes a process for preparing an alkylamide phase for reversed phase HPLC, the bonding reaction being performed after equilibrating the silica with 50% relative humidity to provide the optimal horizontal polymerization reaction and not using a relative humidity below 50% because that provides less than optimal coverage of the silica surface with silanes. However, this is not the claimed invention. Further, Huang in view of Fairbank *teaches away* from the pending claims because it suggests that using a relative humidity below 50% results in poor silica coverage and poor performance characteristics in chromatographic applications. In contrast, the claimed invention provides excellent retention characteristics, stability and reproducibility, resulting from the superior methods of preparation, which are not characteristics of the compositions taught by the prior art references. Applicant respectfully submits that the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41 over Huang in view of Fairbank is overcome and respectfully requests withdrawal of the rejection.

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Claims 9-15, 23 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank as applied to claims 1-6, 8-15, 19, 23, 24, 40 and 41 above and further in view of Neue. The Examiner stated that at best, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank in reciting endcapping. The Examiner further stated that Neue discloses endcapping supports modified by polar silanes reduces undesirable interaction with unmodified silanols. According to the Examiner, it would have been obvious to endcap in each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in view of Karger and Fairbank because Neue discloses endcapping supports modified by polar silanes reduces undesirable interaction with unmodified silanols.

Applicant respectfully traverses this rejection. In contrast to the Examiner's assertion, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in additional respects than reciting endcapping. In addition, the addition of endcapping to the combination of Abbott, Cabrera, Neue, Nau, Liu, and Huang with Karger or Fairbank or Neue would not render obvious the pending claims. As discussed above regarding the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41, Applicant has discovered and developed stationary phases for use in chromatographic applications that exhibit superior and unexpected results, both in terms of superior stability to harsh chromatographic conditions and in terms of superior chromatographic performance. In particular, the presently claimed invention provides superior results in the form of superior peak shapes, superior analyte separations, superior stability to *acidic and basic* solvent conditions, and superior chromatographic characteristics. The stationary phases developed by Applicant exhibit, *inter alia*, superior peak symmetry, with a total absence of tailing and peak asymmetry that is so problematic in other bonded phases, an almost undetectable affinity for base relative to alcohol, remarkable selectivity between basic analytes, low residual silanol activity, and base deactivation. The stationary phases of the instant specification were tested for stability *at both pH 1.5 and at pH 10* for at least 1500 hours and showed superior stability: the variation in retention times, peak symmetry and retention factors was less than 3% for 1000 hours, and less than 5% for 3000 hours, and thus demonstrate greater stability than the compositions of the prior art cited by the Examiner. In addition, the presently claimed stationary phases are prepared using methods that closely control the amount of water on the substrate surface that can participate in the silanization reaction, thereby

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providing superior reproducibility in preparation of the phases, as well as superior reaction control, thereby providing superior stability and low residual silanol activity. *These superior and unexpected results are not taught by the prior art compositions and methods cited.*

Even with the addition of endcapping, to the extent taught by the prior art references, the presently claimed invention provides superior results over the cited references. Thus the present claims are patentable over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank as applied to claims 1-6, 8-15, 19, 23, 24, 40 and 41 above and further in view of Neue, when applied alone or in combination. Applicant respectfully submits that the rejection of claims 9-15, 23 and 24 over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank and further in view of Neue is overcome and respectfully requests withdrawal of the rejection.

Claims 11 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank and Neue as applied to claims 9-15, 23, and 24 above and further in view of Kirkland (U.S. Patent No. 5,869,724, hereinafter "Kirkland"). The Examiner stated that at best, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank and Neue in reciting use of a mixture of silanes. The Examiner further stated that Kirkland discloses that it is desirable to double endcap by dimethylsilylation and trimethylsilylation. According to the Examiner, it would have been obvious to use a mixture of endcapping silanes in each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in view of Karger and Fairbank and Neue because Kirkland discloses that it is desirable to double endcap by dimethylsilylation and trimethylsilylation.

Applicant respectfully traverses this rejection. In contrast to the Examiner's assertion, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in additional respects than reciting use of a mixture of endcapping silanes. In addition, the combination of Abbott, Cabrera, Neue, Nau, Liu, and Huang with Karger or Fairbank or Neue or further in view of Kirkland would not render obvious the pending claims.

Kirkland describes asymmetric bidentate silane reagents for modifying the surface of liquid chromatography supports. Kirkland further teaches the use of the bidentate ligands to provide spacing between C₁₈ alkyl groups so as to avoid aggregation, and that reaction with a bidentate silane

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is desirable to reduce degradation of silica, i.e., that the use of the bidentate ligands provides a more stable support. Use of endcapping and double endcapping is described. However, the addition of Kirkland and the description of a mixture of endcapping silanes does not render the claims obvious.

In contrast to the Examiner's assertion, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in additional respects than reciting a mixture of endcapping silanes. In addition, the addition of a mixture of endcapping silanes to the combination of Abbott, Cabrera, Neue, Nau, Liu, and Huang with Karger or Fairbank or Neue and further in view of Kirkland would not render obvious the pending claims. As discussed above regarding the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41, Applicant has discovered and developed stationary phases for use in chromatographic applications that exhibit superior and unexpected results, both in terms of superior stability to harsh chromatographic conditions and in terms of superior chromatographic performance. In particular, the presently claimed invention provides superior results in the form of superior peak shapes, superior analyte separations, superior stability to *acidic and basic* solvent conditions, and superior chromatographic characteristics. The stationary phases developed by Applicant exhibit, *inter alia*, superior peak symmetry, with a total absence of tailing and peak asymmetry that is so problematic in other bonded phases, an almost undetectable affinity for base relative to alcohol, remarkable selectivity between basic analytes, low residual silanol activity, and base deactivation. The stationary phases of the instant specification were tested for stability *at both pH 1.5 and at pH 10* for at least 1500 hours and showed superior stability: the variation in retention times, peak symmetry and retention factors was less than 3% for 1000 hours, and less than 5% for 3000 hours, and thus demonstrate greater stability than the compositions of the prior art cited by the Examiner. In addition, the presently claimed stationary phases are prepared using methods that closely control the amount of water on the substrate surface that can participate in the silanization reaction, thereby providing superior reproducibility in preparation of the phases, as well as superior reaction control, thereby providing superior stability and low residual silanol activity. *These superior and unexpected results are not taught by the prior art compositions and methods cited.*

Even with the addition of a mixture of endcapping silanes, to the extent taught by the prior art references, the presently claimed invention provides superior results over the cited references. Thus the present claims are patentable over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in

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view of Karger and Fairbank and Neue as applied to claims 9-15, 23, and 24 above and further in view of Kirkland, when applied alone or in combination. Applicant respectfully submits that the rejection of claims 11 and 24 over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank and Neue further in view of Kirkland is overcome and respectfully requests withdrawal of the rejection.

Claims 20-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger as applied to claims 1-6, 8-15, 19, 23, 24, 40 and 41 above and further in view of either Cabrera or Ng (U.S. Patent No. 6,296,768, hereinafter "Ng"). The Examiner stated that at best, the claims differ from each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger and Fairbank in reciting use of cyclodextrin. The Examiner further stated that Ng discloses use of cyclodextrin ligands allows for efficient bulk/industrial scale enantioseparations, and that Cabrera discloses that use of cyclodextrin as a ligand yields improved separation of enantiomers by chromatography. According to the Examiner, it would have been obvious to use a cyclodextrin in each of Abbott, Cabrera, Neue, Nau, Liu, and Huang in view of Karger and Fairbank either because Ng discloses use of cyclodextrin ligands allows for efficient bulk/industrial scale enantioseparations, or because Cabrera discloses that use of cyclodextrin as a ligand yields improved separation of enantiomers by chromatography.

Ng describes chiral stationary phases comprising a support and regiodefined derivatized cyclodextrin chemically bonded via single or double urethane linkages, applicable to HPLC, etc. using a process based on reaction of pre-synthesized regiodefined per-functionalized mono- or di-azidocyclodextrin with primary amines.

Applicant respectfully traverses this rejection, and respectfully requests that the Examiner withdraw the rejections and allow the claims to issue. The addition of Cabrera or Ng does not teach or suggest the superior chromatographic characteristics of the claimed compositions, already discussed above. Applicant has discovered through diligent efforts a method of preparing stationary phases possessing superior separation and stability characteristics, which are not taught by the prior art, alone or in combination. Even if Ng discloses that use of cyclodextrin ligands allows for efficient bulk/industrial scale enantioseparations, and Cabrera discloses that use of cyclodextrin as a ligand yields improved separation of enantiomers by chromatography, the addition of Cabrera or Ng

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to the already extensive list of references of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger cannot render the pending claims obvious.

As discussed above regarding the rejection of claims 1-6, 8-15, 19, 23, 24, 40 and 41, Applicant has discovered and developed stationary phases for use in chromatographic applications that exhibit superior and unexpected results, both in terms of superior stability to harsh chromatographic conditions and in terms of superior chromatographic performance. In particular, the presently claimed invention provides superior and unexpected results in the form of superior peak shapes, superior analyte separations, superior stability to *acidic and basic* solvent conditions, and superior chromatographic characteristics. The stationary phases developed by Applicant exhibit, *inter alia*, superior peak symmetry, with a total absence of tailing and peak asymmetry that is so problematic in other bonded phases, an almost undetectable affinity for base relative to alcohol, remarkable selectivity between basic analytes, low residual silanol activity, and base deactivation. The stationary phases of the instant specification were tested for stability *at both pH 1.5 and at pH 10* for at least 1500 hours and showed superior stability: the variation in retention times, peak symmetry and retention factors was less than 3% for 1000 hours, and less than 5% for 3000 hours, and thus demonstrate greater stability than the compositions of the prior art cited by the Examiner. In addition, the presently claimed stationary phases are prepared using methods that closely control the amount of water on the substrate surface that can participate in the silanization reaction, thereby providing superior reproducibility in preparation of the phases, as well as superior reaction control, thereby providing superior stability and low residual silanol activity. *These superior and unexpected results are not taught by the prior art compositions and methods cited.*

Even with the addition of cyclodextrin, to the extent taught by the prior art references, the presently claimed invention provides superior results over the cited references. Thus the present claims are patentable over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger as applied to claims 1-6, 8-15, 19, 23, 24, 40 and 41 above and further in view of either Cabrera or Ng, when applied either alone or in combination. Applicant respectfully submits that the rejection of claims 20-22 over each of Abbott, Cabrera, Neue, Nau, Liu and Huang in view of Karger as applied to claims 1-6, 8-15, 19, 23, 24, 40 and 41 above and further in view of either Cabrera or Ng is overcome and respectfully requests withdrawal of the rejection.

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IV. INFORMATION DISCLOSURE STATEMENTS:

In the previous submission, Applicant complied with the provisions of 37 C.F.R. §§ 1.56, 1.97(b) and 1.97(e), and submitted Information Disclosure Statements making of record the references cited in the International Search Report in the corresponding PCT application, and additional references that may be pertinent to this application. Applicant acknowledges with appreciation that the Examiner has considered the cited references submitted in the Information Disclosure Statement and made them of record in this application.

CONCLUSION


Entry of this Amendment is respectfully requested. Applicant respectfully submits that the application is in condition for allowance. Favorable consideration is respectfully requested in view of the Amendments and Remarks.

If the Examiner has any questions concerning this communication, or would like to discuss the application, the art, or other pertinent matters, he is welcome to contact the undersigned attorney at (650) 565-8185.

Respectfully submitted,

Date: 1-27-06

By:


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